Nanoparticulate Drug Delivery – Fantasy to Reality

a report by

Jack Aurora

Senior Director, Research and Development, Perrigo Company

Nanoparticles as one of the most effective drug-carrier systems were first described by Speiser and co-workers. Since then, a considerable amount of research focusing on this type of delivery system has been carried out around the world. Since the early to late 1990s, nanoparticle technology has seen an explosion in terms of research in the pharmaceutical industry due to the necessity of extending patent landscapes and exploring more effective ways of treating clinically serious conditions, including – but not limited to – diagnosis and treatment of cancer and management of cardiovascular and infectious diseases. Since then, the buzz-word in pharmaceutical drug delivery has been nanotechnology. As a result, some of the recent work has already seen the light of day in terms of successful clinical trials, regulatory approvals and new drug products.

In 2001, the US President sanctioned a research budget of US$0.5 billion, with an important focus on this highly sophisticated drug delivery system, through the National Nanotechnology Initiative, and in 2006 US President George W Bush presented his budget for the fiscal year 2007 with US$1.28 billion of funding dedicated to nanotechnology. This is a clear indicator of promising ongoing research success in terms of the use of this technology for treating human beings. Industry analysts predict that annual drug revenue in the nano-pharma market will grow by US$80–200 billion by the year 2015–2020.

Nanotechnology offers an excellent opportunity to address the challenging needs and requirements of the newer drug moieties in order for them to exhibit their targeted therapeutic effect. In addition, nanotechnology will provide a business advantage by granting or extending patent landscape. This can be demonstrated by reviewing the number of US Food and Drug Administration (FDA) approvals over the past few years. New chemical entities (NCEs) accounted for only one in four products approved, with the majority of approvals being reformulations or combinations of already approved products. During 2005, several pharmaceutical companies failed to gain approval for an in-house NCE. This NCE/reformulation imbalance trend seems likely to continue, and by 2008 the sales contribution of reformulated products in the US is forecast to be almost 70–80% of total pharmaceutical revenue. Furthermore, it is well known that for every 10,000 compounds that are screened for potential development as a drug, only one actually becomes available for human usage in the market. Out of a number of hurdles, poor aqueous solubility is one of the attributes that has affected more than half of the compounds failing to see the light of day during the discovery stage. The ultimate goal of a drug delivery system is to deploy medications intact and to specifically target sites through a medium that can control the drug administration by either physiological or chemical triggers. In order to achieve this goal, pharmaceutical researchers are focusing on nanotechnology-based drug delivery technologies.

Nanotechnology in Drug Delivery

Nanotechnology is the manipulation of matter at the molecular or atomic level. Nanoparticles can be categorically defined as colloidal carrier systems of sub-micron size that are made from synthetic or natural polymers. Depending on the manufacturing technique employed, nanoparticles can be either drug-encapsulated or surrounded by polymeric covering. Such drug-loaded particles are suitable for nasal, ocular, mucosal, transdermal and parenteral delivery, as well as for oral delivery, the most preferred route. Clinically, these systems have extensive applications for diagnostic and therapeutic purposes. In addition, reducing the particle size of the drug to nano-scale has the immediate impact of making otherwise poorly soluble and poorly bio-available drugs much more soluble, more biologically available and safer. In the case of simpler nanoparticulate systems, the drug molecule is dissolved, entrapped or encapsulated in the nanoparticles, chemically attached to the polymers or, alternatively, adsorbed to their surface.

According to a recent definition provided by a working group of the European Science Foundation in 2004, ‘nanomedicine’ is built on a complex system of nanometer-scale size ranging from one nanometer to hundreds of nanometers and consisting of at least two components, one of which is an active drug ingredient. Some of the major challenges include targeting the specific cell, tissue or organ, and overcoming biological barriers such as the skin, intestine, respiratory mucosa and the blood–brain barrier, which is represented by the tight brain microvascular endothelium.

The selection of appropriate manufacturing methods for drug-loaded nanoparticles depends on the physico-chemical properties of the drug and the polymer and the intended site and duration of delivery. On the other hand, the formulation conditions will determine the inner structure of these polymeric colloidal systems. Practically speaking, two types of systems with different inner structures are possible:

Jack Aurora is Senior Director of Research and Development for the Perrigo Company. Previously, he was Director of Pharmaceutical Research and Development at Pharmascience, Inc. He also worked as Director of Formulation Development at Labopharm, Inc., a specialty pharmaceutical company focused on controlled-release drug delivery design and development. Dr Aurora also serves as a Consultant to the Council of Healthcare Advisors. His research focuses include the development of controlled-release systems, pelletization technology and nasal formulation development. In the field of controlled-release development, he has one US patent to his credit and another four are in process.
1. matrix type, consisting of oligomer or polymer units; and
2. reservoir type, consisting of an oily core surrounded by a
polymeric coating.

An exhaustive and comprehensive literature summarising the
manufacturing and characterisation technologies is available for
reference and further review.

Nanoparticle delivery systems also play a significant role in the treatment
of cancer due to their enhanced permeability and retention effect. This is
due to the hyperpermeability of tumour vasculature and the lack of
lymphatic drainage. Blood-borne macromolecules and colloidal particles
are preferentially distributed in the tumours after systemic administration.
The concentration of polymer–drug conjugates in tumour tissues can reach
levels up to 10–100-fold higher than would be possible after
administration of the free drug.

Polymer Nanoparticles

Nanoparticles are normally made from synthetic or natural polymers.
The polymers used may also be either biodegradable or non-
biodegradable. An ideal polymer should be biocompatible, biodegradable, sterile, non-pyrogenic and with minimum or no toxicity.
The polymer should also have a high capacity to accommodate the drugs
and protect them from degradation until they are delivered to the target
site. Natural polymers have the distinct advantages of biodegradability
and lack of toxicity, but suffer from reproducibility and well defined
physico-chemical properties. Advances in chemistry and biotechnology
are allowing us to evaluate and explore ways of helping natural polymers
to overcome these drawbacks. Sometimes, nanoparticle surfaces can be
modified with targeting ligands. These are research areas that require
more attention and focus.

Among FDA-approved biodegradable and biocompatible polyesters,
poly(epsilon-caprolactone) (PCL) possesses the unique properties of
higher hydrophobicity and neutral biodegradation end-products that do
not disturb the physiological pH balance of the human body. Low-
molecular-weight PCL (e.g. 10–20kDa) degrades quickly in the biological
environment, especially in the presence of lipase. Therefore, over the
next few years, PCL-based polymers and modifications to grant them
further desirable properties will be a common interest and focus for our
research organisations and institutions.

Specific Applications

Nanoparticle-based-delivery systems exhibit a distinct advantage over
existing colon-delivery systems for the treatment of intestinal mucosa
inflammation therapy. The strategy involves targeting the nanoparticles
to the inflamed areas of intestinal mucosa. This application uses
poly(lactic acid-co-glycolic acid) (PLGA) polymers for targeting inflamed
sites. Natural polymers have the distinct advantages of biodegradability
and protect them from degradation until they are delivered to the target
site. Among FDA-approved biodegradable and biocompatible polyesters,
poly(epsilon-caprolactone) (PCL) possesses the unique properties of
higher hydrophobicity and neutral biodegradation end-products that do
not disturb the physiological pH balance of the human body. Low-
molecular-weight PCL (e.g. 10–20kDa) degrades quickly in the biological
environment, especially in the presence of lipase. Therefore, over the
next few years, PCL-based polymers and modifications to grant them
further desirable properties will be a common interest and focus for our
research organisations and institutions.

Recently, the pulmonary route has been the subject of increased focus
and attention, not only for the treatment of lung diseases such as
asthma, but also for fast and efficient drug delivery into systemic blood
circulation. However, caution needs to be exercised when developing
nanoparticulate technology for this application because the impact of
newer polymers and exotic excipients may have an unknown and
deleterious impact on the airway and respiratory epithelia. The
pulmonary route therefore needs to be studied in depth during
pre-clinical studies in animals before clinical trials in humans are
conducted; as animals are complex models they do provide some
true reflection or confirmation of human absorption at a given
biological barrier. Therefore, additional in vitro models of biological
barriers to aid our understanding of cellular-level absorption are being
employed and studied extensively in order to support expensive and
time-consuming human clinical trials.

It may be worthwhile mentioning here that the surface area of the
alveolar epithelium is estimated to be 100–150m², which is
comparable to that of the intestinal mucosa. Also, the lung’s high
blood perfusion rate and very small alveolar fluid volume of 5–25ml
are in favour of its use as a novel route for the application of drugs.
The alveolar epithelium in the deep lung is one of the thinnest barriers
in the human body: the distance between the airspace and the
capillary blood is only about one micron, and can supposedly be
passed by relatively large molecules.

Commercialised Products

Although a number of pharmaceutical products utilising nano-
technology-based systems are still in their infancy, significant
achievements have been made since the first nanoparticulate product,
Rapamune, was introduced into the US market in 2001. The product
was developed by Elan Corporation using its NanoCrystal technology.
It should be mentioned here that the original formulation of the
immunosuppressant, sirolimus, was previously available in oral solution
dosage form in bottles and sachets and required refrigeration, as well
as reconstitution in water or orange juice. The tablet dosage form
developed using nanoparticulate technology provides patients with
convenient administration and storage.

After the launch of Rapamune and authentication of the research success
findings, six further products have been launched in the US:

- three oral dosage form products using Elan’s NanoCrystal technology:
  - Emend by Merck (2003);
  - Tri-Cor by Abbott (2004); and
  - Megace ES by Par (2005);
- Estrasorb, a topical oestrogen developed by Novavax (2004);
Nanotechnology

- Abraxane, an injectable formulation of paclitaxel (2005); and

Annual sales of the above products are in the range of US$1.3 billion.

Approaches

The recent success of nanoparticulate technology in achieving a number of distinct advantages – namely solubility and absorption characteristics – has created industry-wide awareness of the added value for business and market-competitiveness with nanotechnology. In addition, this success has provided an impetus for pharmaceutical research organisations and institutions to develop additional nanotechnology approaches and applications in order to not only solve the problem of drug delivery effectiveness, but also to survive in the industry arena.

Conversion of nanoparticulate suspensions into solid dosage forms while retaining the functional properties of the nano-suspension is a challenge…

The two most commonly researched approaches are micronisation to sub-micron size and controlled crystallisation. Attrition or micronisation is the approach used by Elan’s Drug Technologies group. It involves wet-milling micron drug crystals to nanometer-size and then stabilising these particles against agglomeration by surface adsorption of stabilisers. Baxter Healthcare is also engaged in developing microfluidisation/homogenisation technologies to generate sub-micron particles specifically for injectable drug delivery.

Controlled crystallisation uses supercritical fluid (SCF) technology, which has been employed in the food industry – e.g. for decaffeinating coffee – for many years, but more recently has begun to be explored for pharmaceutical application. Controlled crystallisation can be by either rapid expansion of supercritical fluid (RESS) or gas antisolvent re-crystallisation (GAS). RESS involves solubilisation of the drug in SCF followed by a rapid reduction in pressure and/or rapid elevation in temperature, causing the solute to emerge from the solution. By careful control and optimisation of the process parameters, the sub-micron particle size can be achieved and reproduced. Lavipharma is one of the few companies that has its own proprietary SCF technology and is engaged in this type of platform research for the development of new products. GAS involves dissolving the drug in supercritical fluid (RESS) or gas antisolvent re-crystallisation (GAS), which is achieved by admixing with the SCF. As with RESS, the processing conditions and parameters are responsible for the generation of sub-micron particle size output. Bradford’s solution-enhanced dispersion by supercritical fluids (SEDS) is an example of GAS technology. In addition to GAS and RESS, there are a number of other applied and hybrid technology platforms for controlled crystallisation, such as Eurand’s Biorise technology and a range of approaches from Eiffel Technologies.

Challenges and Expectations

Nanoparticulate technology has the potential to have an important impact in the near future on the way in which drugs are delivered. The commercial feasibility and reproducibility of these platform technologies for oral, parenteral and/or pulmonary delivery are some of the challenges with this system.

Conversion of nanoparticulate suspensions into solid dosage forms while retaining the functional properties of the nano-suspension is a challenge for our researchers in terms of realising the commercial potential of such obviously attractive systems. In order to arrive at an acceptable solid dosage form, secondary processing methods – such as spray-coating in fluid-bed driers, spray granulation in fluid-bed driers and high shear granulations followed by spray-drying – are currently being explored.

As always, each delivery route presents its own challenges and hardships. However, nanoparticulate technology brings additional complications due to smaller particle size and the additional steps needed to achieve and maintain the sub-micron particle size until delivery to the target site, while also providing affordable handling and processing steps as required throughout the manufacturing process. Under these conditions, combining nanoparticulate technologies with other already established drug delivery technologies may bear rewarding results: combining this technology with other drug delivery technologies such as oral, controlled-release, delayed-release and pulsatile-release will provide both broad and novel delivery opportunities.

Future

We have come a long way since the physicist Richard Feynman first proposed the concept of nanotechnology in his ‘There is plenty of room at the bottom’ speech in 1959. The approval and launch of some nanoparticulate technology products in the US market has demonstrated the excellent potential of this technology for advanced drug delivery systems. Over the next decade, the benefits of solubility and stability enhancement will be more greatly appreciated, as will the implications for patent landscape. The use of the platform technology in the discovery arena may also prove a fertile pathway and will aid in the speedy development of this technology, as complex solubility and bioavailability aspects will be addressed at the early screening stage. Another potential application – biologically active nanoparticles for both disease detection and therapy – may not just be a dream, and may well see the light of day in the future. With the results seen so far and the potential future uses of nanotechnology, it should not be long until we see an explosion of many more therapeutically active delivery systems, which will help to promote health – and also a strong economy.